REMARKS

Claims 11-14, 17-20, 23, 24 and 26 were pending in the subject application. Applicants have canceled claim 18 without prejudice to applicants' right to pursue the subject matter of this claim in a later-filed application. Applicants have also amended claims 11, 17, 19, 23-24 and 26 and added new claim 27. Support for these amendments may be found inter alia in the specification as follows: for the term "biologically active" recited in claims 11, 19 and 23: page 17, lines 2-3; claim 17: page 20, lines 23-26; page 30, line 21; page 36, lines 1-25; and Example 10; claim 26: page 15, lines 23-24; claim 27: previous claim 17. The remaining changes to the claims merely introduce minor grammatical and format changes. In making these amendments, applicants neither concede the correctness of the Examiner's rejections in the December 20, 2002 Final Office Action, nor abandon their right to pursue in a continuing application embodiments of the instant invention no longer claimed in this application. These amendments do not involve any issue of new matter. Therefore, entry of these amendments is respectfully requested such that claims 11-14, 17, 19-20, 23-24, 26 and 27 will be pending.

Claim Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 11-14, 17-20, 23, 24 and 26 under 35 U.S.C. §112, first paragraph because the specification allegedly does not provide enablement for the preparation and use of transgenic animals comprising any and all variants of the claimed cholinesterase genes or assay systems of these animals. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in

scope with these claims.

Applicants note the Examiner's statement that the subject specification is enabling for transgenic mice and frog tadpoles whose genomes comprise a transgene comprising an AChE promoter operatively linked to a DNA sequence encoding a splice variant of human AChE expressing AChE with acetylcholine esterase activity, wherein said sequence is expressed in cells of said mouse and where said mouse or tadpole exhibits changes in its neuromuscular junction structure, or and assay systems of said mouse or tadpole or transgenic nonhuman mammals whose genome comprises a DNA sequence encoding a splice variant of human AChE operably linked to a mammary gland promoter, where expression of the DNA sequence results in the production of detectable levels of enzymatically active AChE in the milk of the mammal.

The Examiner stated that applicants argue that the declaration by Dr. Hermona Soreq states that one of skill at the time of filing would have been able to prepare and use any transgenic animal comprising cholinesterase genes and variants thereof, use such transgenic animals as assay systems and use such transgenic animals for the production of hAChE in the milk produced by such animals. The Examiner noted that in view of Dr. Soreq's statements a scope has been made to a nonhuman mammal producing hAChE in its milk. The Examiner stated that the claims encompassing the bioreactor need to be written such that the claimed animal has use as a producer of hAChE. The Examiner stated that as of now there is no promoter to direct mammary gland expression, which does not have to be a mammary gland specific promoter, or that the protein is produced or secreted into the milk of the mammal. The Examiner stated that as written the present claims do not have an enabled use.

The Examiner stated that, however, with regard to the production of animal models for the study of the role of AChE in the development of the nervous system, more than mere expression is required for the claimed animals to have an enabled use. The Examiner stated that there needs to be some effect on the progenitor cells of the nervous system or the outcome of nervous system development. The Examiner stated that the mere presence of the transgene in the cells of the animal is not going to have any effect at all on nervous system development.

The Examiner stated that Dr. Soreq states at paragraph 4(A) that the specification provides guidance as to the making and using of transgenic animals comprising any and all variants of the cholinesterase genes or assay systems of these animals. The Examiner takes issue with this statement as the animals to be used either as a bioreactor or an assay system must express the cholinesterase to some effective level. The Examiner stated that for a bioreactor the effective level would be detectable active enzyme in the milk. The Examiner stated that for the developmental model, some effect of overexpression on the nervous system. The Examiner stated that the present claims only require the animal to have the DNA sequence in its cells.

The Examiner stated that Dr. Soreq states at paragraph 4(B) that cholinesterases neither require membrane structure or glycosylation for esterase activity. The Examiner stated that, however, in view of the art references cited in the previous office action, which express conclusions opposite to declarant, more than a conclusionary statement is needed. The Examiner stated the declarant needs to provide discussion or evidence as to why the references are incorrect.

The Examiner stated that Dr. Soreq states at paragraph 4(C) that animals bearing variants of hAChE present a number of phenotypes beyond changes in neuromuscular junction structure. The Examiner stated that she has no issue with this statement, for the animals to be used as an assay, there must some assayable phenotype. The Examiner stated that for Xenopus tadpoles and mice, as exemplified, the only common phenotype, at least as far as the Examiner could find, is the changes in neuromuscular junction structure.

The Examiner stated that with regard to declarant's additional statements in paragraphs 5-8, the issues are the same. The Examiner stated that the specification discloses two types of animals, Xenopus tadpoles and mice, which show nervous system developmental abnormalities, and mice as a bioreactor. The Examiner stated that with regard to the mice and tadpoles as nervous system developmental models, more than mere expression is required. The Examiner stated that the specification provides no guidance as to how to use the animal models without an assayable endpoint. The Examiner stated that the art at the time of filing taught that the production of transgenic animals with any specific phenotype was unpredictable. The Examiner stated that with respect to the bioreactor claims, such would be found allowable if crafted on the order of the scope of the rejection above. The Examiner noted that the only bioreactor contemplated is a mammary/milk bioreactor.

In a January 15, 2004 telephone conference between Examiner Crouch and Ms. Maria Marucci of the undersigned attorney's office, the Examiner stated that the above rejection of the pending claims may be overcome by amending claim 11 to recite

"biologically active variants of AChE and BChE". In addition, the Examiner stated that with respect to the bioreactor claims, amendment of the claims as she suggested in the December 20, 2002 Final Office Action would be found allowable. In addition, the Examiner stated that claims directed to a transgenic mammal, would probably be allowable.

Claims 11-14 ("developmental model" claims)

In response, applicants respectfully traverse. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 11 to recite in part "biologically active variants". Therefore, the pending claims no longer encompass any and all variants of cholinesterase enzymes.

In addition, the Examiner required an assayable phenotype for the claimed transgenic animals. Without conceding the correctness of the Examiner's position applicants have further amended claim 11 such that it now recites in relevant part: "...wherein the nucleic acid is expressed in the germ cells and somatic cells of the transgenic animal at a higher level relative to a nontransgenic animal." Applicants point out that the determination of whether an animal expresses the transgene is described by many different assays in the subject application. For example, one of skill in the art may use the method of tail (or any other tissue) DNA restriction analysis and blot hybridization as described by applicants at page 74, line 13-page 75, line 31 to determine if a transgene is being expressed in an animal. Therefore, one of skill in the art will be able to readily make and use the transgenic animals claimed by applicants.

Finally, with respect to the Examiner's assertion that Dr. Soreq merely made conclusory statements in her declaration, applicants respectfully traverse. The Examiner appears to have overlooked Dr. Soreq's discussion at paragraph 6 on page 4 of the declaration in support of her opinion. In paragraph 6 of the declaration, Dr. Soreq does indeed cite evidence published by others which supports her point that cholinesterase enzyme requires neither membrane structure or glycosylation for enzyme activity.

In light of the above amendments and remarks applicants maintain that claim 11 and the claims dependent thereon are enabled as required under 35 U.S.C. §112, first paragraph.

Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

Claims 17-20, 23, 24 and 26 ("bioreactor claims")

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claim 18 without prejudice or disclaimer to their right to pursue this claim in a later-filed application.

In addition, applicants respectfully traverse the Examiner's rejection, and maintain that the specification fully enables the preparation and use of transgenic animals comprising biologically active variants of cholinesterase genes; assay systems of the transgenic animals; and production of said cholinesterase genes

in the milk produced by the transgenic animals.

Applicants point out that claim 17 has been amended such that it now recites a promoter which directs expression of the cholinesterase enzyme or biologically active variants thereof to the mammary glands of the transgenic mammal. Therefore, applicants contend that claim 17, amended as suggested by the Examiner, and claims 19-20, 23, 24, 26 and 27 which depend therefrom, meet the requirements of 35 U.S.C. §112, first paragraph. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. § 1.56, applicants would like to direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit B**). A copy of each of the below listed references is attached hereto as **Exhibits 1-3**, respectively.

1. Erb, C. et al. (2000) "Anticholinesterases Intensify the Stress-Induced Alternative Splicing of Acetylcholinesterase mRNA Through M1 Muscarinic Receptors", Neuroscience Letters, Supplement 55, Abstracts of the 9th Meeting of The Israel Society for Neurosciences: S16 **(Exhibit 1)**;

2. Shoham, S. et al. (2000) "Transgenic Acetylcholinesterase Over-Expression Increases Weight Loss Response To Dietary Restriction", Neuroscience Letters, Supplement 55, Abstracts of the 9th Meeting of The Israel Society for Neurosciences: S16 **(Exhibit 2)**;

and

3. Shohami, E. et al. (2000) "Antisense Prevention of Neuronal Damages Following Head Injury In Mice", J. Mol. Med. 78: 228-236 **(Exhibit 3)**.

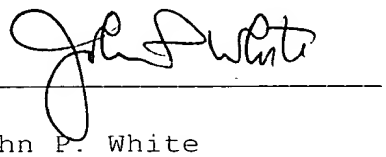
Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 11-14, 17, 19-20, 23-24, 26 and 27.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $1,390.00 sum, which includes the $385.00 fee for filing an RCE and the $1,005.00 fee for a five-month extension of time, is deemed necessary in connection with the filing of this RCE including an Amendment and a Supplemental IDS. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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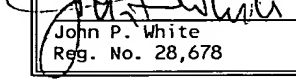
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



1/26/04

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Date